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10/777,683	02/13/2004	Richard B. Moss	Q74236	5880

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EXAMINER	
FOSTER, CHRISTINE E	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/777,683	MOSS ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2007 and 13 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-8,11-15,17,18 and 21-23* is/are pending in the application.

4a) Of the above claim(s) *17,18,22 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-8, 11-15, and 21* is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/11/07 has been entered. Claims 2-3, 9-10, 16, and 19-20 were canceled. Claims 1 and 17-18 were amended. New claims 21-23 were added.

Election/Restrictions

2. Newly submitted claims 22-23, drawn to *methods for assessment of severity and/or acuteness or assessment regarding progress of cystic fibrosis*, do not read on the elected species of *diagnosis* (see the requirement for restriction mailed 9/22/06 and Applicant's election in the Reply of 10/19/06). Accordingly, claims 22-23 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

3. Claims 1, 4-8, 11-15, 17-18, and 21-23 are pending in the application, with claims 17-18 and 22-23 currently withdrawn. Claims 1, 4-8, 11-15, and 21 are subject to examination below.

Objections/Rejections Withdrawn

4. The rejections of claims 2-3, 9-10, 16, and 19-20 and the objections to claims 2 and 19-20 are moot in light of the claims' cancellation.

5. The rejections of claims 1, 4-8, and 11-15 under § 112, 1st paragraph (new matter, written description, and enablement) as set forth in the previous Office action have been obviated by the instant amendments to claim 1. However, the amendments have necessitated new grounds of rejection under this statute as detailed below.

Claim Objections

6. Claim 1 is objected to because of the following informalities:

7. It is suggested that in the first instance of the abbreviation "CAP 18" in the claims that the abbreviation be accompanied by the full term.

8. In claim 1, it is suggested that line 6 refer to "said native CAP 18" rather than "said CAP 18" in light of the prior reference to "native CAP 18" in line 3. Similarly, it is suggested that lines 6-7 refer to "the level of native CAP18".

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1, 4-8, 11-15, and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New Matter

11. Claim 1, as amended in the Reply of 10/11/07, now includes the step of:

> genotypically or phenotypically confirming the diagnosis or the determination of the presence or absence of risk or assessment of the level of the risk.

Applicant indicates in the Reply of 11/13/07 that support may be found for the noted limitation at page 2 of the specification, and also argues the limitation is inherent in the disclosure (see page 2 of the Reply).

The specification at page 2 discloses that:

> Conventionally known diagnosis methods for CF have typically been established on the basis of either genotypic features of CF (CFTR mutations) or phenotypic features of CF (sweat electrolyte value). However, there remains a need for a more accurate, highly sensitive, more convenient, quicker, and inexpensive assessment method for facilitated control of CF (assessment of severity or acuteness of CF, assessment of the degree of progress of CF, etc.).

This is the only mention of any reference to "genotypic" or "phenotypic" methodology found in the specification, and it notably appears in a discussion of prior art methods. There is nothing that would convey that such prior art methods of CF diagnosis are meant to be incorporated into Applicant's methods, as now claimed. In particular, there is no disclosure that such prior art methodology should be used as a confirmatory step in combination with Applicant's CAP 18 measurement methods, for the purpose of confirming diagnosis, risk, or level of risk.

The mention of genotypic or phenotypic-based methodology only in a discussion of the prior art serves to distinguish such methodology from Applicant's invention, rather than convey

evidence of possession of the hybrid methods now claimed that incorporate both the prior art and Applicant's CAP 18 measurement-based methods.

In addition, the above passage only discusses *CFTR mutations* as a genotypic feature and *sweat electrolyte value* as a phenotypic feature. By contrast, the claims have broadened the scope of the original disclosure in that they would encompass genotypes other than CFTR mutations and phenotypes other than sweat electrolyte values. One skilled in the art would not envisage possession of all methods of "genotypically or phenotypically confirming" since the specification only discloses a single species reading on each of these.

Furthermore, the above passage only discusses the use of CFTR mutations and sweat electrolyte values in the context of diagnosis of CF. By contrast, the claims now recite that such prior art methods can be applied not only for diagnosis but also for determining the presence or absence of risk or assessment of the level of risk.

Applicant has argued that the limitation is inherent in the disclosure; however, the noted limitation is an active method step that is performed as part of the claimed methods of diagnosis. Since such a method step would not necessarily and always be performed in conjunction with CAP 18 measurements, support could also not be found by the Examiner in the form of inherent disclosure.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 1, 4-8, and 11-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

14. Independent claim 1 recites a method of measuring the level of "native CAP 18". However, the use of the designation "CAP 18" alone to describe a particular protein renders the claims indefinite because different laboratories may use the same laboratory designation to define completely distinct proteins or protein fragments. This is true in the instant case: the specification states that the entire amino acid sequence of human CAP 18 is given as SEQ ID NO:4 (see p. 7), which is a 170-amino acid protein. However, Montelaro et al. (US 6,835,713 B2) describe human CAP 18 (hCAP18) as being a 37-amino acid peptide (see column 1, lines 57-61). By contrast, Applicant's postfiling work (Xiao et al., discussed above) identifies human CAP18 as a 140-amino acid protein (see p. 2317, left column, the first paragraph). As such, it is not clear what species is being detected since the claim refers only to "native CAP 18" but does not adequately identify the sequence of the protein to be detected.

Although the claim now refers to "native" CAP 18, this descriptor fails to clarify the scope of the claim since the specification indicates that the term "native" refers simply to "non-mutated" CAP 18 (page 7, penultimate paragraph). However, the metes and bounds of the claims cannot be determined since it is not clear whether "native CAP 18" would refer to a non-mutated 37-amino acid peptide, a non-mutated 140-amino acid protein, etc. Amendment of the claims to recite the SEQ ID NO (as in dependent claim 21) may obviate this rejection.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 1, 4-7, 11-14, and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Bals et al. ("Salt-Independent Abnormality of Antimicrobial Activity in Cystic Fibrosis Airway Surface Fluid" *Am. J. Respir. Cell Mol. Biol.* **25** (2001), p. 21-25) and in light of the evidence of iHOP (Information Hyperlinked over Proteins – data for CAMP, cathelicidin antimicrobial peptide, p. 1, downloaded from http://www.ihop-net.org/UniPub/iHOP/gs/86912.html on 01/04/2007).

Bals et al. teach measuring the level of CAP 18 ("LL-37/hCAP-18") in biological samples from humans (bronchoalveolar lavage fluid and human bronchial xenografts generated from respiratory epithelial cells of children) and comparing the levels in cystic fibrosis patients with those of normal control patients (see the entire document, in particular the abstract; p. 21, right column; p. 22, left column; Figures 3-4; and p. 23-24, "Concentrations of Known Antimicrobial Peptides Are Equivalent in CF and Normal ASF").

Bals et al. further teach characterizing the genotype of the cystic fibrosis patients for mutations (page 21, BALFs from CF and non-CF Patients"), which reads on the instantly claimed step of "genotypically or phenotypically confirming the diagnosis".

The protein detected by Bals et al. (LL-37/hCAP-18) anticipates the claim limitation of being "CAP 18" in light of the evidence of iHOP, which teaches that hCAP-18, CAP-18, and

LL37 are synonyms that designate the same protein (p. 1, top right). The protein measured by Bals et al. would also be native (i.e., non-mutated) since the reference refers to the CAP 18 protein present *in vivo* in human BALF samples, for example, as in the instant specification.

Bals et al. compared CAP 18 levels in cystic fibrosis and healthy control subjects (Figures 3-4), and note that the difference was not statistically significant. However, the teachings of Bals et al. read on the claims for the following reasons.

Claim 1 recites steps in which levels of CAP 18 are measured and compared to those in controls and concludes that "whereby an increase in the level of CAP 18 in the biological sample as compared to the control indicates a possible diagnosis...for cystic lung fibrosis".

It is noted that this "whereby" clause does not clearly require any additional active method steps to be performed, and may be interpreted as simply stating a characterization or conclusion of the steps that precede it. The indicated clause does not further limit the claim scope since while it may suggest or invoke steps relating to the assignment or diagnosis of the patient as possibly having cystic lung fibrosis, it does not actually require such steps to be performed. See MPEP 2111.04 and Texas Instruments, Inc. v. International Trade Comm., 988 F.2d 1165, 1171, 26 USPQ2d 1018, 1023 (Fed Cir. 1993) ("A 'whereby' clause that merely states the result of the limitations in the claim adds nothing to the patentability or substance of the claim."). See also Minton v. National Assoc. of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003) ("A whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.").

In addition, the indicated "whereby" clause may also be interpreted simply as a descriptive statement of an inherent property, i.e. that CAP 18 is a possible diagnostic marker for cystic lung fibrosis.

Furthermore, it is apparent in Figure 4 in particular that there were nonetheless differences between control and cystic fibrosis samples. Specifically, Figures 4A and 4B depict increased concentrations of LL-37/hCAP-18 in the cystic fibrosis group (hatched lines) as compared to the control group (shaded boxes without hatched lines). Thus, despite the fact that Bals et al. conclude that the difference was not significant, it is clear that an increase was in fact observed. Thus, an increase over control levels as taught in Bals et al. may be said to suggest or indicate that the subject has cystic fibrosis.

For all of these reasons, given the broadest reasonable interpretation of the claims the teachings of Bals et al. are anticipatory even though the reference does not specifically mention assigning patients with a possible diagnosis of cystic lung fibrosis based on increased CAP 18 levels.

With respect to claim 4, the measurement of CAP18 was via antigen-antibody reaction using polyclonal antisera (se p. 21, right column, "Preparation of Antibodies..." and p. 22, left column, "Determination of Peptide Concentrations...").

With respect to claim 5, Bals et al. teach an antibody raised against LL-37/hCAP-18 containing the C-terminal 37 amino acids (see p. 21, right column, "Preparation of Antibodies..."). As can be seen in the instant sequence listing for the entire amino acid sequence of CAP 18 provided by Applicant as SEQ ID NO:4, SEQ ID NO: 1 is included within the last 37 residues of the protein (see the sequence listing filed 9/20/04). Therefore, the 37-residue peptide

taught by Bals et al. is "a peptide having an amino acid sequence of SEQ ID NO:1", and the antibodies raised thereto would bind to the peptide.

With respect to claim 6, the samples were blotted onto a nitrocellulose membrane (i.e. solid phase) and then probed with the above antisera (page 22, left column, "Determination of Peptide Concentrations...").

With respect to claim 7, Bals et al. teach blotting the sample onto the solid phase so as to immobilize the CAP 18, adding the polyclonal antibody specific for CAP 18 to form a complex, and detecting the complex using a secondary peroxidase-labeled antibody (p. 22, left column, "Determination of Peptide Concentration..." and Figure 4).

With respect to claim 21, which recites that the CAP 18 protein detected consists of SEQ ID NO:4, the instant specification indicates that SEQ ID NO:4 refers to the entire amino acid sequence of human CAP 18. Bals et al. teach detection of human CAP 18 in the same type of sample (BALF) as in the instant application. Furthermore, Bals et al. also teach detection of the protein using an antibody raised against the same portion of SEQ ID NO:4 as Applicant's disclosed antibodies against SEQ ID NOs1-3 (SEQ ID NOs1-3 all fall within the 37 amino acid sequence used to raise the antisera of Bals, as discussed above). Therefore, since Bals et al. detect the same protein using antibodies of the same specificity in the same sample source, there is a strong scientific basis to believe that the methods of Bals et al. also necessarily detects CAP 18 consisting of SEQ ID NO:4, even though the reference does not provide the specific sequence of the CAP 18 protein detected. Absent evidence that the prior art method would not necessarily detect SEQ ID NO:4, the reference reads on the claim. See MPEP 2112 (IV).

Claims 11-14 are taught by Bals et al. as discussed with respect to claims 5-7 above.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 8 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bals et al. in view of Weinberg et al. (US 6,187,536 B1) and in light of the evidence of iHOP.

Bals et al. is as discussed above, which teaches methods for measuring CAP 18 by dot-blot and immunoblot assay. However, the reference fails to specifically teach measuring CAP 18 using a sandwich-type, two-antibody immunoassay as recited.

However, such immunoassay formats were well known in the art at the time of the invention; for example, Weinberg et al. teach immunoassays comprising the steps of bringing into contact a solid phase support in which a first anti-protein antibody is immobilized with a test sample to form a complex or "sandwich" (see column 21, line 44 to column 22, line 7).

Subsequently, the complex is detected either via a detectable second antibody or a third detectable antibody. Weinberg et al. teach that in contrast with simple immunoassays such as dot blot or Western blot, "two-site" or "sandwich" assays as detailed above provide excellent results and can be made quantitative.

Therefore, it would have been obvious to one of ordinary skill in the art to employ the sandwich immunoassay format taught by Weinberg et al., using two CAP 18-specific antibodies, in order to measure CAP 18 in the method of Bals et al. because Weinberg et al. teach that such immunoassays provide excellent results as compared with simple dot blot or Western blot assays, which are the methods used in Bals et al.

Response to Arguments

20. Applicant's arguments in the Reply of 10/11/07 have been fully considered.

21. With respect to the rejection of claim 1 under § 112, 2nd paragraph as being indefinite in reciting "CAP 18", Applicant argues that the amendments to recite "native CAP 18" have addressed the rejection (Reply, page 13). This is not found persuasive because as discussed in the rejection above, the specification indicates that the adjective "native" indicates simply that the protein is non-mutated" (page 7, penultimate paragraph). Indicating that the sequence is non-mutated therefore fails to clarify the scope of the claims, since it is still not clear what sequence(s) and size(s) the proteins falling within the scope of the claim would have.

22. With respect to the rejections under § 102 as being anticipated by Bals et al., Applicant argues (see the paragraph bridging pages 13-14 of the Reply) that breadth is not indefiniteness, which is not on point because such remarks appear to be directed to matters of definiteness of

claim terminology rather than to anticipation. Applicant also argues that the instant amendments have obviated the rejection, to which the Examiner disagrees for reasons detailed in the body of the rejection above.

23. With respect to the rejections under § 103 as being unpatentable over Bals et al., as best understood Applicant argues that Bals et al. teaches away and that the instant amendments to recite a correlation step have obviated the grounds of rejection (Reply, page 14). This is not found persuasive because as detailed above, the recited correlation step is not found to further limit the scope of the claim. Therefore, whether Bals et al. teaches away from diagnosis of cystic fibrosis based on measurement of CAP 18 is moot since the claims do not clearly recite or require any steps in which such a diagnosis is conferred on a patient based on CAP 18 levels.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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